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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,945	12/05/2001	Cheryl Ann Janson	O50937	3771

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 12/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,945	JANSON ET AL.	
	Examiner	Art Unit	
	David J Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *8-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9/15/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

[1] Claims 1-27 are pending.

[2] Applicants' amendment to the specification to incorporate a claim for domestic priority in the amendment filed September 15, 2003, is acknowledged.

[3] Receipt of an Information Disclosure Statement filed September 15, 2003 is acknowledged.

Lack of Unity

[4] Applicants' election with traverse of Group I, claims 1-7, drawn to the special technical feature of a composition comprising an *E. coli* FabH in crystalline form, an *E. coli* FabH crystal, and a selenomethionine mutant crystal of an *E. coli* FabH in the amendment filed September 15, 2003 is acknowledged. Applicants traverse the lack of unity by arguing that Inventions I-VI are not independent because the search terms for one invention will be shared by the others and a search for the additional inventions would not be a significant burden on the examiner. Applicants' argument is not found persuasive.

It is noted that the examiner's assertion that Inventions I-VI do not share a special technical feature is undisputed by applicants. To the extent the lack of unity is made under 35 USC § 121, it is noted that, with the exception of Inventions I and V, none of the inventions requires a patent and non-patent literature text search for an *E. coli* FabH protein crystal. Instead, the claims are drawn to products and methods that

require a text search using terms that would not be required for a search of Inventions I and V. Regarding Inventions I and V, each of these inventions requires a separate patent and non-patent literature search as a search for each of the inventions would require independent considerations, which would require the examiner to focus on different features. For example, a search for Invention V requires a search for a method of solving a crystal form of a mutant, homologue or co-complex of an *E. coli* FabH by molecular rearrangement, which clearly entails a differently structured text search of the patent and non-patent literature than that required for Invention I. Therefore, contrary to applicants' assertion, the search for Invention I requires a different field of search from Inventions II-VI.

Priority

[5] Applicant's claim for domestic priority under 35 USC § 119(e) to provisional application number 60/138,124, filed June 07, 1999 is acknowledged. It is noted that a crystal of purified *E. coli* FabH of SEQ ID NO:1 having an orthorhombic space group symmetry of $P2_12_12_1$ and the unit cell dimensions of a=63.1 Å, b=65.1 Å, and c=166.5 Å and a crystal of purified *E. coli* FabH of SEQ ID NO:1 with methionine replaced with selenomethionine complexed with acetyl-CoA having a tetragonal space group symmetry of $P4_12_12$ and the unit cell dimensions of a=b=72.4 Å and c=102.8 Å are disclosed in 60/138,124 (see page 67-68 of the provisional application).

Specification/Informalities

[6] The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "Crystallization of *Escherichia coli* FabH".

[7] The specification is objected as being confusing in that it refers to Figure 2 as being a graphical representation of a plasmid and a cloning strategy (page 40, lines 10-11 and page 41, line 16) and refers to Figure 3 as being a representation of a PAGE analysis of proteins (see page 42, lines 7-9). However, Figure 2 as filed is a listing of atomic coordinates and Figure 3 is a 3-D representation of an *E. coli* FabH dimer as described in the "Brief Description of Drawings" section at page 2 of the specification.

Claim Objections

[8] Claim(s) 1, 3-4, and 6-7 are objected to because of the following informalities: (1) the term "a *E. coli*" in claims 1, 4, and 6-7 is grammatically incorrect and should be replaced with, for example, "an *E. coli*" and (2) claim 3 does not end with a period. Appropriate correction is required.

[9] Claim 4 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[10] Claim(s) 1-7 is/are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claims 1-4 and 6-7 are indefinite in the recitation of "FabH" as the specification fails to disclose those identifying characteristics of a FabH polypeptide that distinguish the polypeptide from other condensing enzymes. Furthermore, claim 3 refers to specific amino acids of a protein sequence, which requires a reference sequence to determine the recited amino acid positions – in this case, no reference sequence is recited in the claims. It is suggested that, for example, applicants identify the recited "*E. coli* FabH" by a sequence identifier.

[b] Claim 5 is confusing as Table II (pages 13-26 of the specification) "provides the distances between (D) atoms of the active site residues that are within 5.0 angstroms of one another as defined by Table I" and does not provide atomic coordinates as indicated by the claim.

[c] Claim 5 is confusing in the recitation of "the group consisting of the coordinates of Figures 1-2 and Tables I, II, and III. It is unclear as to whether the claim is meant to be interpreted as the FabH of Figures 1-2 or the FabH of Tables I, II, and III OR if the claim is meant to be interpreted as the FabH of Figure 1, Figure 2, Table I, Table II, or Table III. As each of Figures 1 and 2 or Table I and III presents coordinates of a different protein, protein fragment, or

protein complex, the examiner has interpreted the claim as having the latter meaning and the claim has been examined accordingly.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[11] Claim(s) 1-7 is/are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim(s) 1-5 is/are drawn to a composition comprising a genus of *E. coli* FabH crystals. Claim 6 is drawn to a genus of *E. coli* FabH crystals. Claim 7 is drawn to a genus of selenomethionine mutant crystals of *E. coli* FabH.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a *representative number of species* by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. MPEP § 2163

states that a "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only a single representative species of the recited genus of *E. coli* FabH crystals, i.e., a crystal of purified *E. coli* FabH of SEQ ID NO:1 having an orthorhombic space group symmetry of $P2_12_12_1$ and the unit cell dimensions of a=63.1 Å, b=65.1 Å, and c=166.5 Å and discloses only a single representative species of the recited genus of selenomethionine mutant crystals of *E. coli* FabH, i.e., a crystal of purified *E. coli* FabH of SEQ ID NO:1 with methionine replaced with selenomethionine complexed with acetyl-CoA having a tetragonal space group symmetry of $P4_12_12$ and the unit cell dimensions of a=b=72.4 Å and c=102.8 Å. The specification fails to describe any additional representative species of the recited genus of *E. coli* FabH crystals or mutants or selenomethionine mutants thereof as encompassed by the claims. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus", it also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus". In this case, the genus of recited crystals encompasses widely variant species. For example, Davies et al. (*Structure Fold Des* 8:185-195) discloses two crystal forms of *E. coli* FabH complexed with acetyl-CoA. The crystals were generated using identical methods, however, while the crystals display the same space group symmetry, the crystals have very different unit cell dimensions (see page 193, right

column, bottom). Also, Qiu et al. (*J Mol Biol* 307:341-356) report a crystal of uncomplexed *E. coli* FabH that interestingly has a nearly identical space group symmetry and unit cell dimensions to the *E. coli* FabH *complexed with acetyl-CoA* of Davies et al. (page 344, left column, bottom). These examples demonstrate the variation among the species of claimed crystals. The claimed genus of crystals encompasses species that are widely variant in amino acid sequence in complex with or without any binding agent (e.g., any molecule able to co-crystallize with *E. coli* FabH), and having any crystal structure. As such, the disclosure of representative species of a crystal of purified *E. coli* FabH of SEQ ID NO:1 having an orthorhombic space group symmetry of $P2_12_12_1$ and the unit cell dimensions of a=63.1 Å, b=65.1 Å, and c=166.5 Å and a crystal of purified *E. coli* FabH of SEQ ID NO:1 with methionine replaced with selenomethionine complexed with acetyl-CoA having a tetragonal space group symmetry of $P4_12_12$ and the unit cell dimensions of a=b=72.4 Å and c=102.8 Å is insufficient to be representative of the attributes and features of *all* species encompassed by the recited genus. Given the lack of description of a representative number of species, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[12] Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a crystal of purified *E. coli* FabH of SEQ ID NO:1 having an orthorhombic space group symmetry of $P2_12_12_1$ and the unit cell dimensions of a=63.1 Å, b=65.1 Å, and c=166.5 Å and a crystal of purified *E. coli* FabH of SEQ ID

NO:1 with methionine replaced with selenomethionine complexed with acetyl-CoA having a tetragonal space group symmetry of $P4_12_12$ and the unit cell dimensions of a=b=72.4 Å and c=102.8 Å, does not reasonably provide enablement for all *E. coli* FabH crystals, compositions thereof, or selenomethionine mutant crystals of *E. coli* FabH. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation would be required for a skilled artisan to make the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

- The claims are overly broad in scope: The claims are so broad as to encompass all *E. coli* FabH crystals, compositions thereof, or selenomethionine mutant crystals of *E. coli* FabH. There is no indication in the specification that an *E. coli* FabH crystal is meant to be interpreted as a crystal of the *E. coli* FabH of SEQ ID NO:1. Instead, the specification indicates that the claims are so broad as to encompass mutants and

variants of the *E. coli* FabH of SEQ ID NO:1 (see page 34 of the specification). The broad scope of claimed crystals and compositions is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of protein crystals broadly encompassed by the claims. In this case the disclosure is limited to a crystal of purified *E. coli* FabH of SEQ ID NO:1 having an orthorhombic space group symmetry of $P2_12_12_1$ and the unit cell dimensions of a=63.1 Å, b=65.1 Å, and c=166.5 Å and a crystal of purified *E. coli* FabH of SEQ ID NO:1 with methionine replaced with selenomethionine complexed with acetyl-CoA having a tetragonal space group symmetry of $P4_12_12$ and the unit cell dimensions of a=b=72.4 Å and c=102.8 Å.

- The lack of guidance and working examples: The specification provides the working examples of a crystal of purified *E. coli* FabH of SEQ ID NO:1 having an orthorhombic space group symmetry of $P2_12_12_1$ and the unit cell dimensions of a=63.1 Å, b=65.1 Å, and c=166.5 Å and a crystal of purified *E. coli* FabH of SEQ ID NO:1 with methionine replaced with selenomethionine complexed with acetyl-CoA having a tetragonal space group symmetry of $P4_12_12$ and the unit cell dimensions of a=b=72.4 Å and c=102.8 Å produced by the methods set forth at page 47 of the specification. These working examples fail to provide the necessary guidance for making the entire scope of crystals and compositions as broadly encompassed by the claims. The specification fails to provide guidance regarding crystallization of other compositions comprising *E. coli* FabH or mutants thereof (e.g., *E. coli* FabH complexed with any molecule that binds thereto), or alterations in the crystallization method with an expectation of obtaining diffraction quality crystals.

- The high degree of unpredictability in the art is supported by the state of the art: Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999) teaches that protein crystallization is usually quite difficult to achieve and the formation of protein crystals is critically dependent on a number of different parameters, including pH, temperature, protein concentration, the nature of the solvent and precipitant, as well as the presence of added ions and ligands to the protein (page 375, middle). Branden et al. teach that even small changes in the crystallization parameters, e.g., pH, can cause the molecules to pack in different ways to produce different crystal forms (page 375, bottom). Thus, even minor modifications to a crystallization method may result in crystals that are distinct in structure having different space group symmetry and unit cell dimensions. Furthermore, alteration of an amino acid sequence by mutagenesis or replacement of methionine with selenomethionine in a given protein alters the amino acid and chemical composition of the protein. Thus, when crystallized, such variants and selenomethionine mutants may pack differently forming different crystals from that of the protein of SEQ ID NO:1, even under identical crystallization conditions. Even crystals generated using the same crystallization method may be different. For example, Davies et al. (*Structure Fold Des* 8:185-195) discloses two crystal forms of *E. coli* FabH complexed with acetyl-CoA. The crystals were generated using identical methods, however, while the display the same space group symmetry, the crystals have very different unit cell dimensions (see page 193, right column, bottom). Thus, crystallization of the same protein under identical conditions may generate different crystals. Furthermore, Qiu et al. (*J Mol Biol* 307:341-

356) report a crystal of uncomplexed *E. coli* FabH that interestingly has nearly identical space group symmetry and unit cell dimensions to the *E. coli* FabH *complexed with acetyl-CoA* (page 344, left column, bottom). Also, Daines et al. (*J Med Chem* 46:5-8) disclose that attempts to co-crystallize *E. coli* FabH with a specific inhibitor were unsuccessful due to the poor solubility of the inhibitor (page 5, right column, bottom). These examples demonstrate the high degree of unpredictability associated with protein crystallization. In this case, the specification fails to provide sufficient guidance and/or working examples to predictably make the broad scope of recited crystals and compositions. Thus, a skilled artisan would recognize the high degree of unpredictability in generating the broad scope of claimed crystals.

- The amount of experimentation required is undue: While methods of protein crystallization are known, it is *not* routine in the art to make all crystals as broadly encompassed by the claims. Thus, in view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high degree of unpredictability as evidenced by the prior art, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention.

Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological

characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Conclusion

[13] Status of the claims:

- Claims 1-27 are pending.
- Claims 8-27 are withdrawn from consideration.
- Claims 1-7 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The Examiner can normally be reached Monday-Friday from 7:00 am to 5:00 pm. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for submission of official papers to Group 1600 is (703) 308-4242. Draft or informal FAX communications should be directed to (703) 746-5078. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.
Patent Examiner
Art Unit 1652

12-03-03
DAVID STEADMAN
PATENT EXAMINER